REMARKS

Status of the Claims

Claims 8, 9, 14, 15 and 32 are pending in the application. Claims 8, 9, 14, 15 and 32 are rejected. Claim 9 is amended herein. No new matter is added to the amended claim.

Claim amendment

Claim 9 is amended herein to overcome the 35 U.S.C. §112, first paragraph rejection. Amended claim 9 limits the cell-cell interaction inhibited in the independent claim 8 to one that is mediated by the $\alpha v\beta 3$ and/or $\alpha 5\beta 1$ integrin ligand. This amendment is supported by Examples 15-29 of the instant invention.

The 35 U.S.C. §112 Rejection

Claims 8-9, 14 and 15 are rejected under 35 U.S.C. §112, first paragraph as not being enabling. Applicants respectfully traverse this rejection.

The Examiner states that the specification is enabling for inhibiting cell-cell interaction or inhibiting tumor growth using antibodies directed against the sequence consisting of either SEQ ID NO: 41 or SEQ ID NO: 2, where the sequences are derived from a peptide of SEQ ID NO: 14, but is not enabling for inhibiting cell-cell interaction or inhibiting tumor growth using antibodies directed against the sequence consisting of either SEQ ID NO: 41 or SEQ ID NO: 2, where the sequences are derived from a peptide of SEQ ID NO: 13. Furthermore, the Examiner states, that the specification does not provide sufficient enablement to inhibit cell-cell interaction such as the one that contributes to inflammation associated with infection, ischemia reperfusion injury, endotoxin lethality, arthiritis etc.

The Applicants submit that the instant invention identifies the role of vascular endothelial growth factor and type I collagen inducible protein (VCIP) in cell-cell interactions and demonstrates that the cell-cell interaction are integrin mediated and that the RGD motif present in VCIP acts as a cell-associated integrin ligand (Example 15-18). The integrin mediated cell-cell interaction involving VCIP could also contribute to

inflammation. The instant invention also investigated the contribution of VCIP-RGD in adhesion of endothelial cells to extracellular matrix (Example 19). Further, the instant invention demonstrates the crucial role of the RGD motif present in VCIP in cell-cell interaction and angiogenesis by using mutant constructs of VCIP, bearing a RGE motif instead of RGD, transfected into HEK293 cells. The cells expressing RGE motif containing VCIIP did not form aggregates, while the cells expressing the RGD-motif containing VCIP, successfully formed aggregates (Example 14). Hence, the instant invention demonstrates that VCIP the RGD-motif containing domain of is crucial for it to mediate cell-cell interaction involving integrins and thus inflammation.

Applicant respectfully disagrees with the Examiner's argument that sequence of VCIP from which the peptides of SEQ ID NO: 2 and 41 are derived is SEQ ID NO: 14. Applicant reiterates that the instant invention demonstrated that incubation of cells (HEK293) expressing wild type VCIP with peptides that comprised RGD motif or with anti-VCIP-RGD antibody generated using the peptide of SEQ ID No. 2 inhibited cell-cell interaction (Example 14; Table 1). The peptide with SEQ ID No. 2 comprises amino acids 173-192 of the VCIP with SEQ ID No. 13. The VCIP with SEQ ID No. 14 just represents the phosphatase domain of human VCIP (Lipid phosphatase domain). This phosphatase domain comprises amino acids 145-161 of the VCIP with SEQ ID No. 13 and does not include the RGD domain. Hence, the peptide with SEQ ID NO: 2 and SEQ ID No: 41 cannot be derived from VCIP with SEQ ID No. 14 as both these sequences contain the RGD motif. Therefore, Applicant reiterates that the VCIP in the instant claims is the one with SEQ ID No. 13.

Further, with regard to the contention made by the Examiner that the specification does not provide sufficient enablement to inhibit cell-cell interaction such as the one that contributes to inflammation associated with infection, ischemia reperfusion injury, endotoxin lethality, arthiritis etc., Applicants submit that the claims of the instant invention are directed towards inhibiting inflammation by disrupting cell-cell interaction mediated via the RGD-motif containing VCIP and the alphavb3 and alpha5b1 integrins. Hence, it is understood that the inflammation inhibited is due to the interaction of the proteins discussed supra. The instant invention does not claim inhibiting inflammation mediated by mechanisms other than an interaction between VCIP and the alphavb3 and

alpha5b1 integrins. Claim 8 clearly recites that the instant invention is directed towards a method of inhibiting cell-cell interaction by blocking the interaction between VCIP and the alphavb3 and alpha5b1 integrins. Claim 9 is amended herein to specifically recite the alphavb3 and alpha5b1 ligands. Claim 14 is dependent from claim 8 and thus limits the cause of the inflammation to the interaction between VCIP and the integrins discussed supra. Thus, the scope of the claimed invention is commensurate with the scope of enablement provided. Accordingly, based on the arguments and remarks presented supra, Applicant respectfully request the rejection of claims 8-9, 14 and 15 under 35 U.S.C. §112, first paragraph be withdrawn.

The 35 U.S.C. §102 Rejection

Claims 8-9, 14-15 and 32 are rejected under 35 U.S.C. §102(a) as being anticipated by **Humtsoe** *et al* (April 2003). Applicants respectfully traverse this rejection.

The Examiner states that **Humtsoe** *et al* teach a method of inhibiting cell-cell interaction comprising contacting the cells with anti-VCIP-RGD antibody. Humtsoe et al teach dose-dependent inhibition of cell aggregates in response to the anti-VCIP-RGD (claimed SEQ ID NO:2 and 41) antibody. Further, the Examiner states that **Humtsoe** *et al* teach that the cell-cell interaction contributes to normal as well as unwanted cell cycle progression, vascular malformation, expansion of atherosclerotic lesion, invasion and growth of solid tumor.

The Applicants submit respectfully that the provisional application was filed March 27, 2003 before the reference claimed by the Examiner as prior art (published April 2003), and thus the instant invention claims benefit of priority. For these reasons, Humtsoe et al cannot be used as prior art for rejection under 35 U.S.C. §102(a). Accordingly, Applicants respectfully request that the rejection of the claims 8-9, 14-15 and 32 under 35 U.S.C. §102(a) be withdrawn.

Claims 8-9 and 14-15 stand rejected under 35 U.S.C. §102(b) as being anticipated by **Vassilev** *et al* (Blood 1999 Jun 1; 93(11):3624-3631) as is evidenced by **Bendayan** (J Histochem Cytochem 1995, 43:881-886). Applicants traverse this rejection.

The Examiner finds the arguments made by the Applicant in the Response After Final non-persuasive for the following reasons: First, that the referenced antibody was not raised against the peptide of 10 amino acid in length but purified by said peptide. Second, that **Vassilev** *et al* teach binding of anti-RGD antibodies to the peptide and to proteins expressing RGD sequence by ELISA (page 3625, 1st col.). Third, that the referenced antibodies were able to bind fibronectin, fibrinogen, vitronection, VWF and laminin in a dose dependent manner. Based on this, the Examiner states that the skilled in the art would expect that the referenced antibody to bind to the sequences of SEQ ID NO: 2, 41 and 13. Hence, the rejection is maintained. Applicant respectfully disagrees.

Vassilev *et al* teaches that the effects of IVIg that contains natural antibodies to many cell surface molecules. **Vassilev** *et al* teach that 0.15% of these pooled antibodies have the ability to bind RGD motif in proteins. These anti-RGD antibodies thus have the ability to inhibit the adhesion several RGD-mediated interactions. **Bendayan** *et al* teach characterization of the specific reactivity of a monoclonal antibody produced to human proinsulin and show that although the antibody is highly specific, it is able to bind not only to human proinsulin but to proinsulin from other species and even a distinct protein based upon the conservation of an Arg-Arg dipeptide sequence in eah of these molecules.

Applicants submit that the instant invention teaches a specific antibody directed against a peptide consisting of SEQ ID No. 41 or consisting of SEQ ID No. 2 that is derived from a cell surface vascular endothelial growth factor and type I collagen inducible protein (VCIP) consisting of SEQ ID No. 13. The antibody taught by the instant invention is able to block binding of $\alpha v\beta 3$ and/or $\alpha 5\beta 1$ integrins to the cell surface vascular endothelial growth factor and type I collagen inducible protein (VCIP), thereby inhibiting the cell-cell interaction. As discussed supra, **Vassilev** *et al* teach a pool of antibodies that are able to bind to a RGD-motif containing protein. However, **Vassilev** *et al* do not identify one antibody in particular that is able to mediate binding to the RGD-motif containing proteins. Further, **Vasilev** *et al* demonstrate that their pool of antibodies can bind to fibronectin, fibrinogen, vitronectin, VWF and laminin in a dose-dependent manner but do not show or demonstrate that it can bind to VCIP. Furthermore, the proteins taught by **Vassilev** *et al* are all basement membrane proteins. It is known in the art that there are many adhesive proteins present in extracellular matrices and in the blood that contain the

tripeptide arginine-glycine-aspartic acid (RGD) as their cell recognition site. The RGD sequences of each of the adhesive proteins are recognized by at least one member of a family of structurally related receptors, integrins. Some of these receptors bind to the RGD sequence of a single adhesion protein only, whereas others recognize groups of them. Thus, the conformation of the RGD sequence in the individual proteins is critical to this recognition specificity. Hence, one of skill in the art cannot assume that the unidentified antibodies in the pool taught by **Vassilev** *et al* would also bind the VCIP protein identified by the instant invention.

In order to anticipate a claim, the prior art reference must teach each and every element of the claim. Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. The instantly claimed methods use a specific antibody directed to "specific peptides", derived from VCIP. It is not inherent based on the teachings of **Vassilev** *et al*, cited by the Examiner, that the unidentified antibodies, that bind RGD-motif containing basement membrane proteins, would also bind the RGD-motif containing VCIP expressed by endothelial cells, given that the conformation of the RGD would be different in VCIP versus the proteins taught by **Vassilev** et al. At a minimum, neither of the references cited by the Examiner teach the antibodies against peptide of SEQ ID NO: 2 or 41 derived from the protein represented by SEQ ID NO: 13. Hence, independent claim 8 and its dependent claims 9 and 14 are not anticipated by **Vassilev** *et al*. Claim 15 is also not anticipated for the same reasons stated *supra*. Accordingly, based on the claim amendments and above-discussed remarks, Applicant respectfully requests the withdrawal of rejection of claims 8-9 and 14 under 35 U.S.C. §102(b).

The 35 U.S.C. §103 Rejection

Claims 15 and 32 stand rejected under 35 U.S.C §103(a) as being unpatentable over **U.S. Patent No. 5,807,819** in view of **U.S. Patent No. 5,567,440** and **Vassilev** *et al* as is evidenced by **Bendayan**. Applicant respectfully traverses this rejection.

The Examiner finds the arguments made by the Applicant in the Response After Final non-persuasive for the following reasons: First, the disclosure that the anti-RGD antibodies of **Vassilev** *et al* bind to peptide and to proteins expressing RGD sequences such

as the RGD-containing decapeptide, fn, vitronectin, fg and vWf suggests that the referenced anti-RGD antibodies would bind the claimed RGD-containing sequences of SEQ ID NOs: 2, 41 and 13 in the absence of evidence to the contrary. Second, since **Vassilev** *et al* provide strong evidence that the anti-RGD antibodies bind multiple RGD containing proteins, one of ordinary skill in the art would expect the referenced antibody to bind to the claimed RGD-containing peptides and VCIP protein of SEQ ID NOs: 2, 41 and 13 in the absence of the evidence to the contrary. Third, **Bendayan** teach that the referenced antibodies would bind to the claimed sequences base on the shared RGD motif. **Bendayan** characterizes the specific reactivity of a monoclonal antibody produced to human proinsulin and shows that although the antibody is highly specific, it is nevertheless able to bind to not only human proinsulin but to proinsulin from other species and even a distinct protein, glucagons based on the conservation of an Arg-Arg dipeptide sequence in each of these molecules. Additionally, **Bendayan** conclude that an antibody directed against such a sequence, although still yielding specific labeling, could reveal different molecules not related to the original antigen. Based on all of these reasons, the Examiner contends that the referenced anti-RGD antibodies would bind to the claimed RGD-containing peptides and proteins of SEQ ID Nos: 2, 41 and 13. Applicant respectfully disagrees.

As discussed supra, the instant invention teaches a specific antibody directed against a peptide of SEQ ID No. 41 or SEQ ID No. 2 that is derived from VCIP consisting of SEQ ID NO: 13. This antibody blocks the binding of $\alpha v\beta 3$ and/or $\alpha 5\beta 1$ integrins to the cell surface vascular endothelial growth factor and type I collagen inducible protein (VCIP), thereby inhibiting the cell-cell interaction. **Vassilev** *et al* teach a pool of antibodies that are able to bind RGD-containing protein and to basement proteins such as fibronectin, vitronectin, VWF and laminin in a dose dependent manner. There is no teaching or suggestion in this reference that the antibody would also bind peptide/protein with SEQ ID No: 2, 13 and 41 as taught by the instant invention.

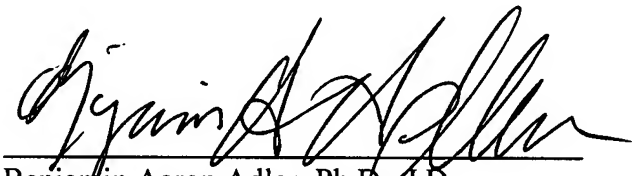
As discussed supra, it is known that the extracellular matrices and blood comprise many adhesive proteins that contain RGD as their recognition site. Applicant respectfullys submits that some of the structurally related receptors such as integrins bind to the RGD sequence of a single adhesion protein whereas others recognize groups of them. Thus, the ability of the receptor to recognize the RGD sequence in the individuals

critically depends on the conformation of the RGD sequence in the individual proteins. This teaching along with the absence of demonstration by **Vassilev** *et al* of their antibodies bind to the instant peptides, Applicant contends that one skilled in the art cannot expect success in merely substituting the antibody of Vassilev et al in the instantly claimed method. Therefore, the instant claims are not prima facie obvious over prior art reference. Accordingly, based on the claim amendments and remarks, Applicant respectfully requests the withdrawal of rejection of claims 15 and 32 stand rejected under 35 U.S.C §103(a).

This is intended to be a complete response to the Office Action mailed March 09, 2007. Applicant encloses a Petition for Extension of time and Form PTO-2038 along with the response. If any issues remain outstanding, please telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

Date: 8/6/07



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